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In Vitro Preparation of Infarcted Myocardium

by Betty I. Sasyniuk*

An isolated ventricular endocardial preparation removed from canine hearts one to two days after coronary artery occlusion and superfused *in vitro* is described. The alteration in electrophysiological characteristics of subendocardial Purkinje fibers surviving in infarcted regions and the relationship of these changes to the generation of ventricular arrhythmias is discussed. The advantages of such preparations for assessing the mechanism of action of antiarrhythmic drugs in post-infarction ventricular arrhythmias is discussed.

Our efforts to understand the basic cellular electrical properties of cardiac muscle has been greatly aided by the use of isolated preparations of cardiac tissue. The use of such preparations permits the investigator to apply direct intracellular recording with glass microelectrodes. Indeed, much of what we know about quantitative cellular electrophysiology has resulted from study of isolated cardiac tissue. This has been due largely to the fact that it is technically difficult to record with glass microelectrodes from single cardiac cells in a beating heart, particularly from Purkinje fibers, since the endocardial surface is not readily accessible.

A major goal of electrophysiological studies in isolated cardiac tissue has been to determine the origin and mechanism of cardiac arrhythmias and their modification by antiarrhythmic drugs. The majority of these studies have been done on essentially normal cardiac tissue isolated from healthy animals. The applicability of information on the mechanism of action of antiarrhythmic drugs obtained from studies on normal cardiac tissue to diseased hearts is questionable. Efforts have been made to simulate a pathological condition by exposing normal tissue to an altered extracellular environment such as hypoxia, or high extracellular potassium concentrations. All of these procedures still represent essentially acute interventions superimposed on normal electrical activity.

In recent years, studies have begun to determine the alteration of electrical properties of cardiac muscle after naturally occurring or experimentally produced pathology. The preparation I shall describe is designed to elucidate the cellular electrophysiological mechanisms underlying the ventricular arrhythmias which accompany myocardial infarction in an attempt to determine the mechanism of action of antiarrhythmic drugs in this setting. This model consists of isolated ventricular tissue excised from infarcted dog hearts and superfused *in vitro* with Tyrode's solution. A similar model has been used by other investigators (*1*, *2*).

Myocardial infarction is produced by simply ligating the left anterior descending coronary artery approximately 1 cm distal to its point of origin under direct visualization in an anesthetized mongrel dog. We employ a two- or three-stage procedure, first producing one or two partial obstructions and then a complete occlusion with a 10- to 15-min interval between occlusions. This method avoids losing too many dogs because of ventricular fibrillation in the first few minutes. If the animal lives, this method produces a fairly predictable infarction, although the size does vary from animal to animal. The animals that survive the early period of ischemia and arrhythmia usually develop single or multiple premature beats within 6 hr after ligation. By 24 hr, a frank tachycardia is present which can last for several days.

One to two days after coronary ligation, the animals are reanaesthetized. The chest is opened through the initial incision, the hearts are rapidly removed and placed in cold oxygenated Tyrode's solution in which they are carefully dissected. The infarcted region can be readily identified by its characteristic pale color. Preparations consisting of

* Department of Pharmacology and Therapeutics, McGill University, 3655 Drummond Street, Montreal, Canada H3G 1Y6.

the septal portion of the anterior division of the left bundle branch, free-running bundle, and anterior papillary muscle together with portions of the intraventricular septum, the paraseptal free wall and the interpapillary free wall are dissected and mounted endocardial surface upwards in a superfusion chamber. Figure 1 shows a typical example of the type of preparation used. The epicardial portion of the preparation is removed to decrease its thickness and to facilitate mounting of the tissue in the superfusion chamber. However, the preparation still consists of a fairly large block of tissue. Preparations are superfused at a rapid rate of 25 ml/min with Tyrode's solution equilibrated with a 95% oxygen–5% carbon dioxide gas mixture. Since the tissue blocks are more than a few hundred microns in diameter, diffusion of electrolyte and oxygen into them will be limited. This fact may be considered a serious drawback of these preparations. However, we are dealing here largely with the subendocardial conducting system of the ventricles which comprises the first one to five layers of subendocardial cells. Superfusion of the conducting system by oxygen-rich superfusate is probably sufficient to keep this tissue functional and is probably comparable to the *in vivo* situation in which surviving endocardial tissue adjacent to a myocardial infarct derives its nutrients from oxygen-rich blood in the left ventricular cavity. In fact, this may be the very reason why it survives.

FIGURE 1. Isolated preparation of infarcted myocardium showing endocardial surface: (FT) free-running false tendon; (APM) anterior papillary muscle; (IPFW) interpapillary free wall; (PSFW) paraseptal free wall; (IVS) interventricular septum; (NP) microelectrode in normal Purkinje fiber; (IP) microelectrode in Purkinje fiber in infarcted zone; (S_1S_2) site of stimulation. The infarcted areas appear pale while the noninfarcted areas appear darker. Ligation of the left anterior descending coronary artery usually produces infarction of the base of the anterior papillary muscle and lower two-thirds of the septum.

Figure 2 shows an example of the alteration in the electrical activity in the infarcted area studied with extracellular electrodes. Bipolar electrograms were recorded from multiple sites on the preparation. With the exception of electrogram A obtained from the free-running false tendon, all electrograms recorded from the noninfarcted areas consisted of two distant deflections corresponding to activity in Purkinje fibers (early rapid deflection), and underlying ventricular muscle (second delayed slow deflection). In contrast to this, most of the electrograms recorded from the infarcted area consisted of only a single deflection suggesting that activity in underlying muscle was absent at most sites within the infarcted area. This was confirmed by recording intracellular potentials from the same areas on the preparation from which bipolar electrograms had been recorded. Compared to normal regions, the number of cells from which action potentials could be recorded at any one site within the infarcted region was markedly diminished. At most sites, potentials could only be recorded from the top one to four layers of cells. Most surviving cells had characteristics of Purkinje fibers. Occasionally ventricular muscle survived either in the top layers or beneath Purkinje fibers. In some areas no activity could be recorded at all.

Purkinje fibers surviving in subendocardial areas of canine infarcts have action potentials which are distinctly abnormal for several days after coronary artery occlusion. Normal cardiac Purkinje fibers typically have high resting membrane potentials and generate fast response action potentials. The resting membrane potential is generally reduced in Purkinje fibers surviving infarction. It is well known that reduction of the resting potential in cardiac cells produces characteristic changes in the transmembrane action potential. Partially depolarized cells (i.e., with resting potentials less than −80 mV but greater than −60mV) generate action potentials with reduced upstroke velocities because of partial inactivation of the fast sodium channel. Such action potentials have been referred to as depressed fast responses (*3*). If the membrane potential is reduced even further (to levels at which the rapid inward sodium current is completely inactivated), slow response action potentials are generated (*3*).

The infarcted area in each preparation usually shows the entire spectrum of action potentials from

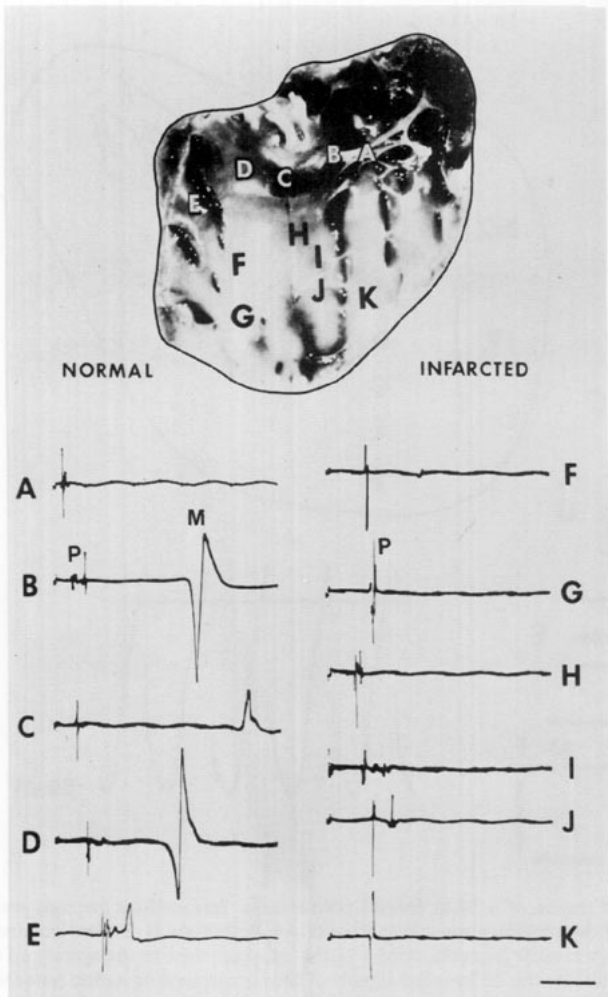

FIGURE 2. Comparison of bipolar electrograms obtained from normal and infarcted regions of a left anterior papillary muscle preparation excised from the left ventricle 24 hr after occlusion of the left anterior descending coronary artery. The preparation was stimulated at a basic cycle length of 600 msec through stimulating electrodes positioned on the septal portion of the anterior bundle. A-E represent bipolar electrograms obtained from multiple sites along the normal portions of the preparation; F-K electrograms from regions which were visibly infarcted. Potentials were recorded simultaneously from two sites. One electrode remained at a fixed site while the other one was used to explore the preparation. P represents activity in Purkinje fibers; M, in ventricular muscle. Extracellular potentials attributed to P or M cells could be verified by intracellular exploration in the vicinity of the extracellular electrodes. Tracing A shows a P electrogram recorded from the free-running bundle. Tracings B to D are typical of patterns recorded near the tip of the papillary muscle where P cells were activated early but underlying M cells are activated much later. Trace E is typical of the type recorded in the normal area where electrical continuity between P and M cells is established. Tracing B in the normal zone and H and J in the infarcted zone show multiple P spikes. Only electrogram I shows evidence of slow muscle activity in the infarcted zone. Tracings F, G, and K show only single P spikes. Calibration 10 msec, 1 mV.

pure fast responses to depressed fast responses to pure slow responses. An area of slow response activity is often surrounded by an area of depressed fast response activity. One characteristic feature of all of these potentials (regardless of their resting potentials) is their markedly prolonged durations. This is illustrated in Figure 3. Action potentials recorded from free-running fibers in the infarcted zone often had phase 0 characteristics which were within normal limits but durations which were markedly prolonged. Surviving muscle cells within the infarcted area also had action potentials with prolonged durations.

In previous models used to study drug effects depressed fast or slow response potentials have been created artificially in the tissue bath by exposure of normal Purkinje fibers to a variety of interventions such as perfusion with a high potassium medium or exposure to a high potassium plus epinephrine medium (*3*). These procedures have been designed to lower resting membrane potential to levels at which the sodium mechanism is partially or totally inactivated and at the same time to induce slow response activity in order to simulate the pathological condition. One disadvantage of such models is that drug effects are studied on pure slow or pure fast responses which normally do not exist as single populations in diseased tissues. There is, instead, a population of cells with an entire spectrum of potentials in which both sodium and calcium currents must contribute to a variable degree to the action potential upstroke and consequently to the occurrence of conduction abnormalities and arrhythmias. An advantage of the present model is that drug effects may be assessed simultaneously on the entire spectrum of action potentials. Thus, a particular drug might be effective to an extent dictated by the ionic currents operating in the individual cardiac fibers overlying the infarcted region.

Table 1 summarizes the important characteristic features of potentials within the infarcted area. These characteristics probably play a role in the genesis of post-infarction ventricular arrhythmias. One important feature of Purkinje fibers surviving infarction in the period beginning approximately 10 hr after coronary artery occlusion is the presence of enhanced automaticity. This enhanced automaticity usually peaks during the first 24 hr after coronary artery occlusion and subsides thereafter, being very low 72 hr after occlusion. Figure 3 shows an example of such activity. The decline in automaticity in these preparations usually coincides with the disappearance of the *in vivo* arrhythmia. Thus assessing the effects of drugs on automaticity in these preparations should provide an indication of their *in vivo* actions.

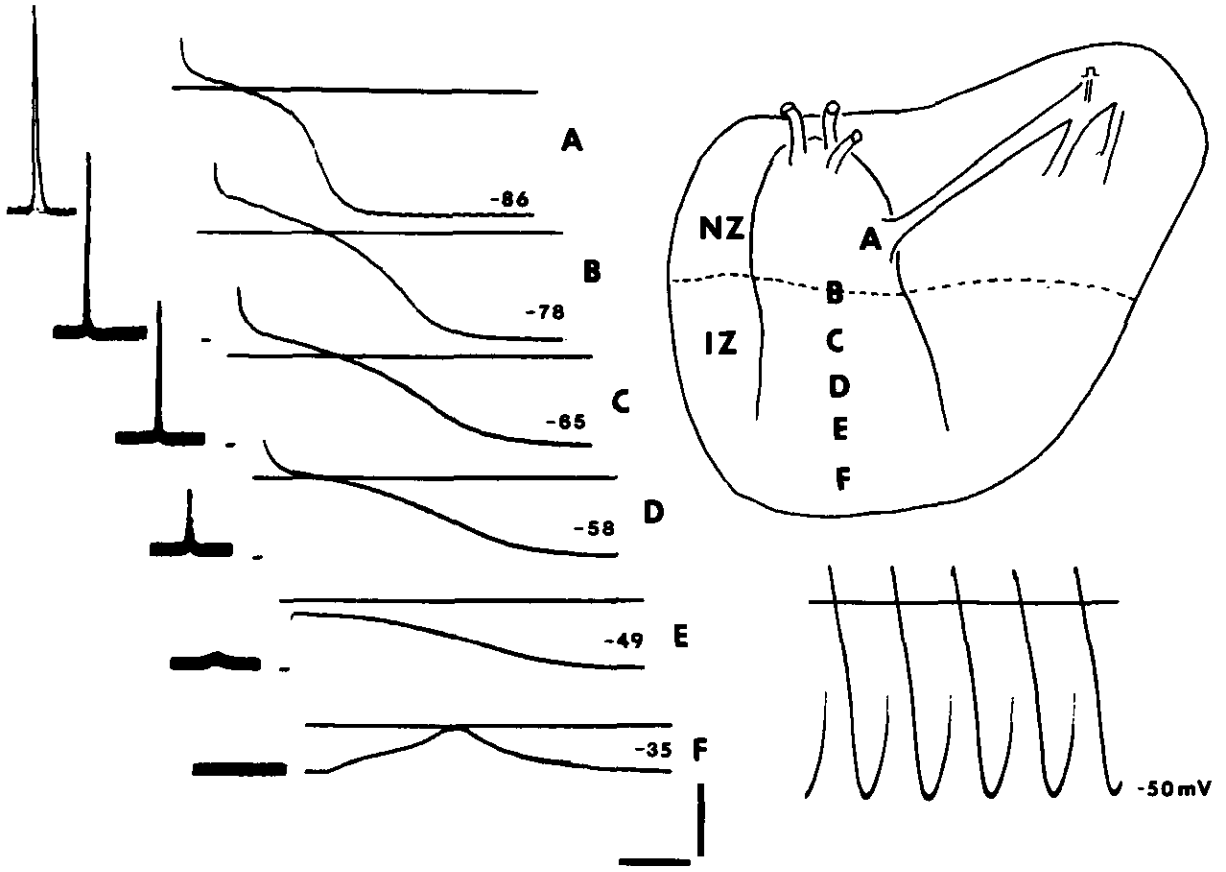

FIGURE 3. Spectrum of intracellular potentials within the infarcted region of a 24 hr infarct preparation. Intracellular records were obtained from a normal Purkinje fiber at the noninfarcted tip of the papillary muscle (potential A). Potentials B–F were obtained from various sites on the infarcted portion of the anterior papillary muscle from the border of the infarcted area to the apical end of the papillary muscle. Traces to the left of the action potentials indicate the differential signals of the corresponding action potential upstrokes. Maximum diastolic potentials and upstroke velocities progressively decreased from the border area to a site deep within the infarcted area. Preparation was stimulated at a basic cycle length of 600 msec. Calibrations: 100 msec, 200 V/sec, 50 mV. Traces below the preparation show an example of automatic activity in the infarcted area when the preparation was not electrically stimulated. Calibrations: 1000 msec, 20 mV.

Table 1. Characteristics of action potentials of subendocardial Purkinje fibers surviving infarction.

1. Phase 0 characteristics	Usually lower than normal; Resting membrane potentials usually less than −75 mV; Accompanied by lower than normal amplitudes and upstroke velocities. Inhomogeneity of phase 0 characteristics ranging from near normal fast response to depressed fast response to slow response type potentials.
2. Duration of action potentials	Abnormally prolonged durations due largely to abnormal prolongation of phase 3. Plateau duration may be normal, prolonged, or abbreviated. Distribution of action potential durations within the ventricular conducting system is altered depending upon location of infarct.
3. Refractory periods	Markedly prolonged; Post-repolarization refractoriness is present to varying degrees
4. Membrane responsiveness	Responsiveness is depressed; Maximum upstroke velocity usually not achieved at full repolarization. Related to either delay in sodium recovery or presence of slow response potentials
5. Conduction velocity	Conduction velocity of premature beats is markedly depressed.
6. Spontaneous activity	Enhanced from about 10 hr, peaks during the first 24 hr and declines thereafter. Enhanced automaticity occurs at extracellular potassium concentrations at which automaticity is generally low in normal Purkinje fibers. Islands of enhanced automaticity may exist showing both entrance and exit block. Triggered activity may be present.

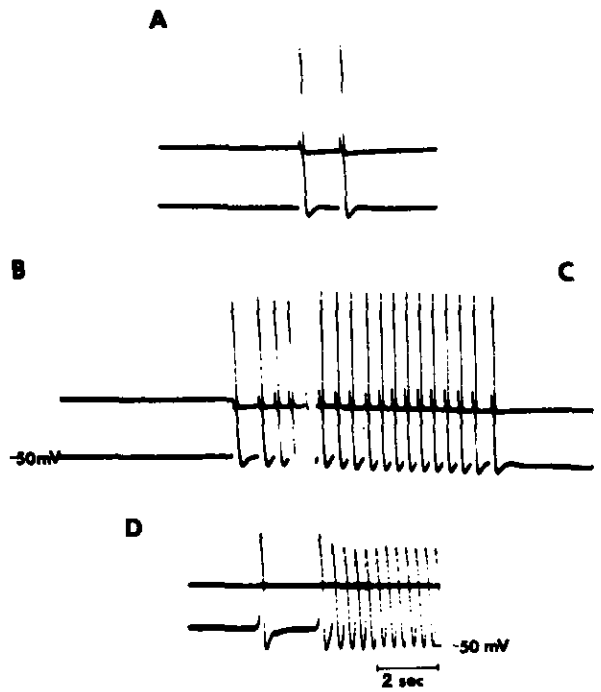

FIGURE 4. Triggered sustained rhythmic activity in a subendocardial Purkinje fiber surviving infarction induced by spontaneously occurring impulses in two different preparations induced 48 hr after coronary artery occlusion.

A, B, C The upper traces show an action potential recorded from a Purkinje fiber in the normal zone; the lower traces show those from a fiber in the infarcted zone with a lower level of resting potential. The potential recorded from the infarcted zone shows an after hyperpolarization followed by a very slow delayed after depolarization. The normal cell shows a slight phase 4 diastolic depolarization. (A) shows two spontaneous potentials occurring in close succession in an otherwise quiescent preparation. The origin of the spontaneous impulses may be the infarcted area since activity in this area precedes activity in the normal area (B) shows initiation of a burst of sustained rhythmic activity following another spontaneous impulse. (C) shows termination of the triggered activity. The last triggered potential is followed by a delayed after depolarization. There is a gradual increase in membrane potential in the infarcted cell prior to termination of triggered activity. (D) shows another example of sustained rhythmic activity following the second of two spontaneous impulses. Both preparations were quiescent with isolated spontaneous beats between periods of triggered activity.

A form of triggered activity can also be demonstrated in the infarcted area. In preparations studied 48 hr after coronary artery occlusion, regular automaticity is not always present. In some preparations long periods of quiescence are interrupted by bursts of sustained rhythmic activity which can last for 20–30 beats or as long as 10 min. Such bursts of rhythmic activity may be initiated by spontaneous impulses as shown in Figure 4 or by driven impulses.

The other changes in action potential characteristics which have important implications for reentry mechanism usually persist beyond the period of *in vivo* arrhythmias but revert to normal by one week post-infarction. The reason for the normalization is not known but may be related to a collateralization of the infarcted myocardium thus reestablishing blood supply to this region.

It is well known that action potential durations and local refractory periods vary along the course of the intraventricular conducting system from the level of the bundle branches to their distal terminations in muscle (*4*, *5*). In anterior papillary muscle preparations action potential durations normally increase progressively from the proximal bundle branches and reach a maximum prior to insertion of the free-running bundle into the papillary muscle (Fig. 5*A*). This region of maximal action potential duration has been referred to by Myerberg et al. as "the gate." As one records distally from the gate region, action potential durations gradually decrease. This normal pattern of distribution of action potential durations is altered in the presence of infarction (Fig. 5*B*). The decrease in action potential duration beyond the gate region is followed instead by a progressive increase in duration in the infarcted region reaching maximum values which greatly exceed the maximum values observed in the noninfarcted portion of the conducting system. The region of longest action potential duration is no longer located in the normal gate area but distally in the infarcted area. This abnormal distribution of action potential durations alters the conduction of premature beats. Very early premature beats initiated in the proximal conducting system would arrive in the infarcted region while the latter was still refractory and either block or be significantly delayed. Such alteration in conduction has important implications for re-entry mechanism. The abnormal distribution of action potential durations reverts to normal by one week after occlusion.

Previous cellular studies in normal tissue have suggested several mechanisms for ectopic rhythms, including among others, accelerated pacemaker activity, triggered activity, and re-entry (*3*). Re-entry has been much more difficult to reproduce in the tissue bath and studies using normal tissue have often required drastic interventions to produce the conditions necessary for such a mechanism to occur, in particular, the requisite slowing in conduction (*3*). These conditions are easily satisfied in infarcted preparations following the introduction of premature beats.

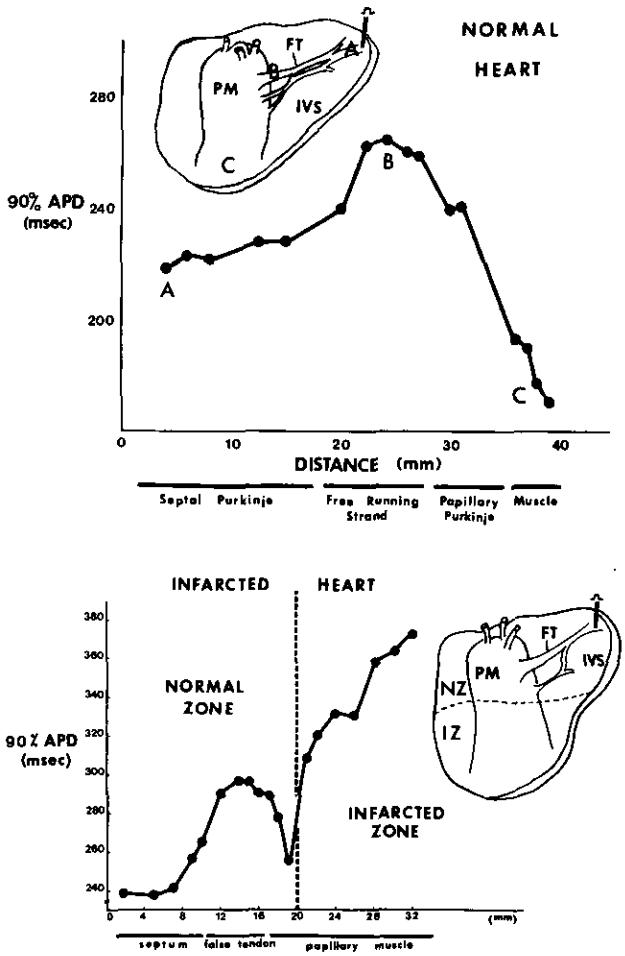

FIGURE 5. Maps of action potential durations at the 90% level of repolarization in the left anterior conducting system: (*a*) normal heart and (A) proximal conducting system; (B) gate region; (C) distal conducting system; (*b*) in a preparation from an infarcted heart. The dashed line indicates the approximate location of the border zone between normal and infarcted areas.

Figure 6 shows an example of the relationship between the prematurity of the response initiated in the proximal conducting system and the delay in activation of the recording site within the infarcted region as it is related to the generation of re-entrant beats. In these experiments, basic and premature stimuli were applied to the proximal conducting system in the normal region. Intracellular potentials were obtained from the normal region close to the stimulating site and from a site well within the infarcted area. Premature stimuli were delivered at progressively decreasing coupling intervals after every tenth basic response. As the coupling interval of the premature impulse was progressively reduced to values less than 300 msec, activation of the recording site within the infarcted area occurred progressively later reaching maximum delays at the shortest coupling intervals. When the premature impulse activated the recording site within the infarcted area with a certain minimal degree of delay, it was consistently followed by unstimulated and presumably re-entrant responses. Such re-entrant responses would likely result in ectopic beats in the whole heart.

We have examined the effects of a number of antiarrhythmic drugs in this model. These studies have helped to elucidate the mechanism of action of these drugs in the setting of infarction. One striking example is the action of bretylium. All previous studies with this drug have been done in preparations removed from normal hearts. Since the only significant action of bretylium was to increase action potential duration in ventricular muscle and Purkinje fibers, without altering the relationship between effective refractory period and action po-

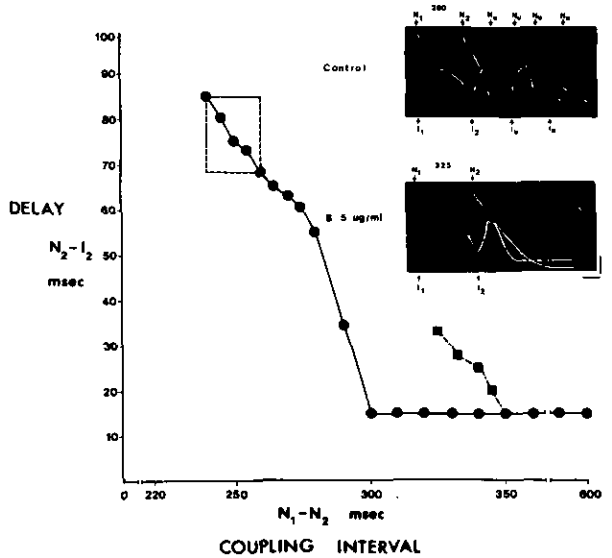

FIGURE 6. Relationship between the coupling interval of the premature response initiated in the proximal conducting system of the non-infarcted zone and the activation delay in the subendocardial Purkinje fiber network in an infarcted left anterior papillary muscle preparation 24 hr after coronary artery occlusion: (●) control; (■) after equilibration with bretylium, 5 μg/ml. The action potentials shown above and to the right of the graph indicate the responses obtained (top) under control conditions and (bottom) after equilibration with 5 μg/ml of drug. The control panel shows unstimulated responses (N_u) following an N_1-N_2 of 260 msec. All premature responses which conducted with delays of 70 msec or greater, were consistently followed by re-entrant responses. The window on the control graph indicates the coupling intervals and activation delays associated with re-entry. In the presence of drug, there is a marked increase in the refractory period of the normal Purkinje fiber. The earliest impulse that could be initiated in the normal area propagated to the infarcted area with a delay of only 33 msec. No unstimulated responses (N_u) occurred in the presence of drug. Calibration: 50 mV and 100 msec.

tential duration, previous investigators concluded that the antiarrhythmic efficacy of bretylium was not due to any intrinsic direct electrophysiologic effect of the drug but most probably related to its adrenergic neuronal blocking actions (*6, 7*).

Our studies suggest that the direct effect of bretylium in prolonging action potential duration may indeed be important for its antiarrhythmic action (*8*). Bretylium produces considerable prolongation of action potential duration of all fibers which is accompanied by a prolongation of the effective refractory period of a similar magnitude. However, an important finding is that the degree of prolongation of action potential duration varies with the location of the fiber within the conducting system. Bretylium produces the greatest degree of prolongation of action potential duration in normal Purkinje fibers in which duration is the shortest to begin with and the least increase in duration in those cells within the infarcted area in which durations are extraordinarily prolonged under control conditions. This action of the drug results in a decrease in the disparity in action potential duration and refractory period between normal and infarcted regions. In the presence of bretylium, the earliest premature impulses which could be initiated in the proximal conducting system arrived in the infarcted region when the latter had more fully recovered its excitability and therefore conducted with a minimum of delay as shown in Figure 6. Thus the degree of delay occurring in the presence of drug was not sufficient to allow surrounding normal tissue to recover its excitability and be re-excited. Consequently re-entry did not occur in the presence of drug. Furthermore, because of the increase in the refractory period of normal tissue surrounding the infarcted region, even greater activation delays than occurred under control conditions would have been required to permit re-entry to occur in the presence of drug. It is apparent that the full significance of the direct electrophysiological effects of bretylium could not have been appreciated from studies in normal hearts.

It is well known that bretylium may produce a transient increase in ventricular arrhythmic activity (*9*). The drug can transiently enhance automaticity in the infarcted area (*8*). Figure 7 shows another mechanism by which bretylium may increase arrhythmic activity in the presence of infarction, i.e., by induction of triggered activity. Bretylium may enhance the amplitude of delayed afterdepolarizations of potentials within the infarcted area and result in sustained rhythmic activity. This effect is probably related to release of norepinephrine from adrenergic nerve terminals by the drug since catecholamines are well known to induce triggered activity (*3*).

There is still considerable controversy over the mechanism of action of lidocaine. Earlier *in vitro* studies in normal tissue claimed that lidocaine did not depress membrane responsiveness or conduction velocity, did not alter excitability and abbreviated refractoriness (*10, 11*). Later studies showed that membrane responsiveness is depressed by the drug, particularly in depolarized cells or in cells exposed to a high extracellular potassium concentration (*12*).

Our studies in infarcted preparations suggest that lidocaine selectively depresses cells within the infarcted region while having minimal effects on phase 0 characteristics in normal Purkinje fibers. Figure 8 shows the differential effects of 2 and 8 μg/ml of drug. Exposure of the preparation to the higher concentration of drug caused tremendous depression of the action potential in the Purkinje fiber surviving infarction while causing only a small depression of phase 0 of the action potential in the fiber in the normal zone.

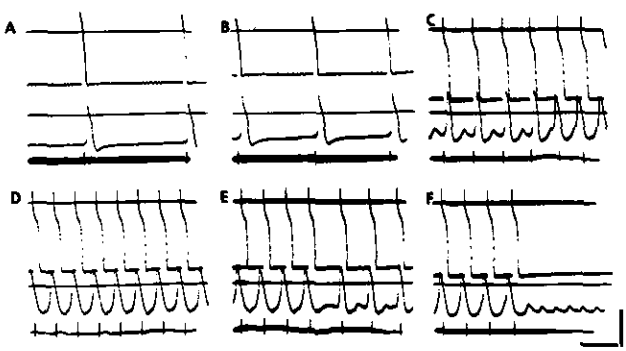

FIGURE 7. Triggered sustained rhythmic activity in a subendocardial Purkinje fiber surviving infarction induced by exposure to bretylium. In each panel records were obtained from a fiber in a noninfarcted area (upper trace) and from a fiber in the infarcted area (lower trace); the bottom trace shows a bipolar electrogram obtained from the border zone. (A) shows control spontaneous activity; the origin of the spontaneous activity may be the normal zone since activity here precedes activity at all other sites. (B) shows an increase in the spontaneous rate 5 min after exposure to 5 μg/ml of bretylium. (C) shows a further increase in the spontaneous rate 8 min after exposure to bretylium. A new normal fiber was impaled. The increase in rate is accompanied by a marked after-depolarization in the infarcted cell. Following the fourth potential the delayed after depolarization reaches threshold and initiates sustained rhythmic activity (D) Continuation of sustained rythmic activity. (E) shows termination of triggered activity several minutes later. The last triggered potential and all subsequent spontaneous potentials are followed by delayed after depolarizations. (F) shows termination of another run of triggered activity 10 min later followed by a delayed after depolarization and oscillatory potentials. During exposure to the drug for 1 hr, periods of triggered activity which lasted from 2 to 10 min were followed by periods of quiescence. Calibrations: 1000 msec. 50 mV.

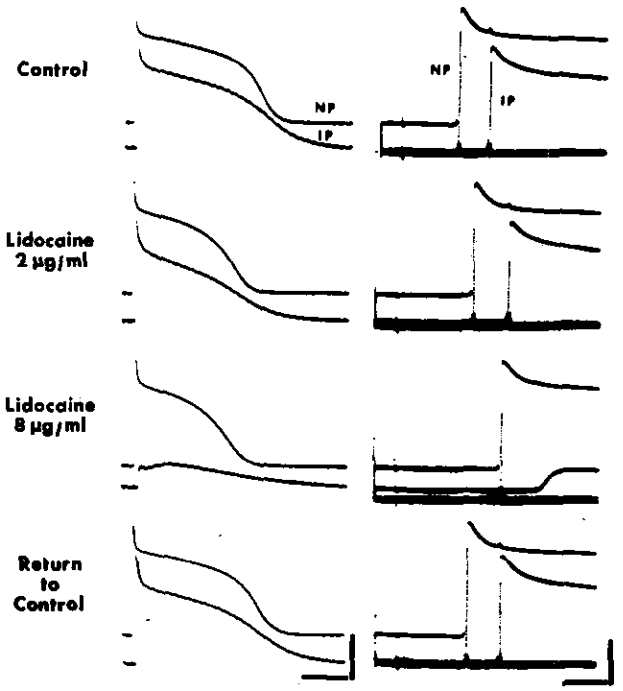

FIGURE 8. Selective depressant effect of lidocaine on the action potential upstroke of a Purkinje fiber surviving infarction. In each panel on the left the upper trace is an intracellular action potential recorded from the normal zone and the lower trace from the infarcted zone. Panels on the right show the same action potentials recorded at a faster sweep speed along with the differentiated signals of the action potential upstrokes. Calibrations: 100 msec, 5 msec, 50 mV, 200 V/sec.

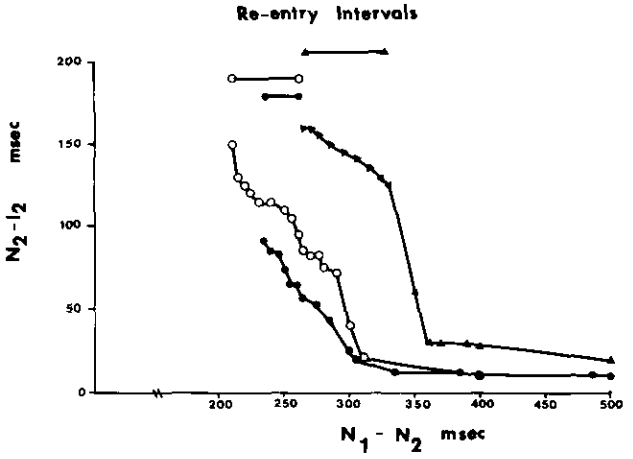

FIGURE 9. Effects of lidocaine on the conduction of premature impulses to the infarcted zone: (●) control; (○) lidocaine, 5 µg/ml; (▲) lidocaine, 10 µg/ml. The graph shows the relationship between the coupling interval (N_1-N_2) of the premature impulse initiated in the proximal normal conducting system and the activation of the most distal recording site within the infarcted zone (N_2-I_2). The horizontal lines above the curves indicate the range of N_1-N_2 coupling intervals over which re-entrant responses occurred under control conditions and in the presence of drug.

The degree of depression of upstroke velocity of action potentials within the infarcted area was related to their initial resting membrane potential. The lower the resting potential in these cells to begin with the greater was the depression by the drug. In cells with low resting potentials not only is there a reduction of the fast inward sodium current but also an increase in the time required for recovery of the sodium mechanism. In Purkinje fibers surviving infarction, unlike normal fibers, maximum upstroke velocity is not attained at full repolarization. Lidocaine not only depresses responsiveness in these cells but further prolongs the time of recovery of maximum upstroke velocity. This latter effect is probably responsible for a prolongation of the refractory period in cells within the infarcted area despite an abbreviation of action potential duration by the drug.

Unlike bretylium, lidocaine markedly slows conduction of premature beats within the infarcted area as illustrated in Figure 9. This figure shows the effect of 5 and 10 µg/ml of drug. Under control conditions, the earliest premature beats which could be initiated in the proximal conducting system conducted to the infarcted zone with considerable delay and were followed by re-entrant responses over a 25-msec range of coupling intervals. Following equilibration with 5 µg/ml of drug even earlier premature impulses could be initiated in the proximal conducting system. There was no change in the conduction of basic impulses but an even greater delay of conduction of premature impulses to the recording site within the infarcted area. In the presence of drug, unstimulated responses occurred over a wider range of coupling intervals. Following exposure to 10 µg/ml, the infarcted region did not respond to early premature impulses. However, premature impulses initiated at later coupling intervals propagated to the infarcted zone with marked delay and were again followed by re-entrant responses. Thus, the selective depressant action of the drug in cells within the infarcted area which might be considered an ideal action for abolishing a re-entry mechanism may in fact have the opposite effect. The crucial factor which determines whether a particular drug effect may be beneficial or not is of course dependent upon a critical balance between conduction velocity and refractory period in a re-entry circuit. Thus whether a particular drug effect tips the balance in favor or against re-entry would depend upon the conditions prevailing in the particular tissue. Lidocaine, in the concentrations used, apparently tips the balance in favour of re-entry.

In contrast to its failure to abolish re-entry mechanism in infarcted preparations, lidocaine was

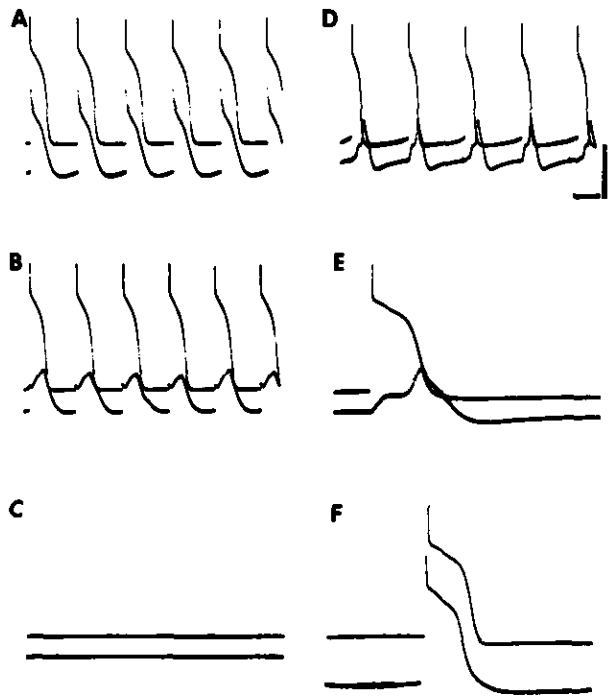

FIGURE 10. Abolition of spontaneous activity in a 24-hr infarct preparation following exposure to 2 μg/ml of lidocaine: (A) control; (B, C) 5 and 10 min after exposure to lidocaine; (D, E) 26 min after return to drug-free perfusion; (F) 10 min after addition of 50 μg of epinephrine to the superfusion chamber. In each panel, the top trace is a record obtained from a normal Purkinje fiber, the lower trace from a Purkinje fiber in the infarcted region showing spontaneous phase 4 diastolic depolarization. Calibrations: 50 mV and 500 msec in A and B; 1000 msec in D, 200 msec in E and F.

very effective in abolishing enhanced spontaneous activity within the infarcted area in small concentrations. This is illustrated in Figure 10, which shows the effect of 2 μg/ml of lidocaine in a fiber within the infarcted area showing enhanced phase 4 diastolic depolarization. Automatic activity originated in the infarcted region. However, another spontaneously depolarizing fiber within this region must have been the true pacemaker. Following exposure to lidocaine the cell within the infarcted area became rapidly depressed while the normal cell was unaffected. This was followed very soon by abrupt cessation of activity. Although diastolic depolarization was abolished in the fiber within the infarcted region it continued to fire at the same rate suggesting that the true pacemaker may not have been affected by the drug and that abolition of spontaneous activity may have been related to exit block around the true pacemaker. Following return to control Tyrode's solution, spontaneous activity originated in the normal area, while the infarcted area was still considerably depressed. If automaticity originated in cells showing slow response activity it would not have been affected by the drug. Thus, a drug which does not alter slow response automaticity may prevent it from influencing the rest of the heart by abolishing activity in depressed fast response fibers which surround an area of slow response activity.

Figure 10 also shows the effect of epinephrine on potentials depressed by lidocaine. Epinephrine did not alter the potential of the normal Purkinje fiber but hyperpolarized and markedly improved the potential recorded from the infarcted zone.

These few examples illustrate the differential effects of various drugs on normal and infarcted potentials in an *in vitro* preparation of infarcted myocardium and point out the hazards of extrapolating drug effects in normal tissue to diseased tissue.

Our results suggest that the use of this kind of *in vitro* preparation with all of the attendant disadvantages of using a superfusion technique does bring us one step closer to understanding the mechanism of arrhythmias in the setting of myocardial infarction and their modification by antiarrhythmic drugs. However, further studies on cardiac muscle from both human and experimentally produced diseased myocardium are necessary for a more complete understanding of the response of clinical arrhythmias to these drugs.

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